

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/485, 31/165, 45/06		A2	(11) International Publication Number: WO 97/04780
			(43) International Publication Date: 13 February 1997 (13.02.97)
(21) International Application Number: PCT/US96/12597			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 31 July 1996 (31.07.96)			
(30) Priority Data: 08/510,546 2 August 1995 (02.08.95) US			
(71) Applicant: VIRGINIA COMMONWEALTH UNIVERSITY [US/US]; Medical College of Virginia, MCV Station, 1200 East Marshall Street, Richmond, VA 23298 (US).			
(72) Inventors: MAYER, David, J.; 502 Honaker Avenue, Richmond, VA 23226 (US). PRICE, Donald, D.; 3316 Loxley Road, Richmond, VA 23227 (US). MAO, Jianren; 1630 Monument Avenue, Richmond, VA 23220 (US). LYLE, John, W.; 28 Inlet Terrace, Belmar, NJ 07719 (US).			
(74) Agents: DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).			Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PAIN-ALLEVIATING DRUG COMPOSITION AND METHOD FOR ALLEVIATING PAIN			
(57) Abstract The analgesic effectiveness of a combination drug containing at least one analgesic is significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist thereto, e.g. dextrometorphan or dextrothorphan.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PAIN-ALLEVIATING DRUG COMPOSITION
AND METHOD FOR ALLEVIATING PAIN

5

BACKGROUND OF THE INVENTION

This invention relates to a pain-alleviating drug composition and method for alleviating pain. The drug composition includes as a first component a first analgesic which may be of the opioid type, e.g., codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, propoxyphene, pentazocine, etc., or of the nonopioid type, e.g., a coal tar analgesic such as acetaminophen or a nonsteroidal antiinflammatory drug (NSAID) such as aspirin or ibuprofen, as a second component, a sedative, e.g., of the barbiturate type such as butalbital or of the nonbarbiturate type such as diphenhydramine, dichloralphenazone, droperidol or promethazine, a skeletal muscle relaxant such as methocarbamol or carisoprodol and, where the first analgesic is of the opioid type, a second analgesic of the nonopioid type, e.g., acetaminophen, aspirin or ibuprofen, and as a third component, a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist such as dextrophan or dextromethorphan.

A number of drug combinations for alleviating pain or treating other conditions associated with a pain component are known including the following: codeine phosphate and acetaminophen; hydrocodone bitartrate and acetaminophen; codeine phosphate and aspirin; hydrocodone bitartrate, acetaminophen, caffeine, chlorpheniramine maleate and phenylephrine hydrochloride; hydrocodone bitartrate and aspirin; dihydrocodeine bitartrate, acetaminophen and caffeine; dihydrocodeine bitartrate, aspirin and caffeine; codeine phosphate and promethazine hydrochloride; meperidine hydrochloride and promethazine hydrochloride; oxycodone hydrochloride and acetaminophen;

oxycodone hydrochloride, oxycodone terephthalate and aspirin; pentazocine hydrochloride and acetaminophen; pentazocine hydrochloride and aspirin; propoxyphene napsylate and acetaminophen; propoxyphene hydrochloride and acetaminophen; propoxyphene hydrochloride, aspirin and caffeine; acetaminophen and diphenhydramine citrate; acetaminophen and diphenhydramine hydrochloride; acetaminophen, dichloralphenazone and isometheptene mucate; aspirin and butalbital; acetaminophen, butalbital and caffeine; aspirin, butalbital and caffeine; codeine phosphate, aspirin, butalbital and caffeine; aspirin and methocarbamol; aspirin and carisoprodol; codeine phosphate, aspirin and carisoprodol; and, fentanyl citrate and droperidol.

The analgesic component(s) of each of these combination drugs can cause adverse reactions. Opioid analgesics such as codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, propoxyphene and pentazocine can produce tolerance and/or dependence. As for the nonopioid analgesics, acetaminophen has been known to cause fatal hepatic damage and the NSAIDs have a tendency to cause gastrointestinal side effects ranging from the relatively mild to the quite severe (ulceration of the stomach or duodenum). The risk of these adverse reactions is all the greater where their long term administration is concerned.

Dextromethorphan is the d-isomer of the codeine analog of levorphanol. Unlike the l-isomer, dextromethorphan is said to have no analgesic or addictive properties (Goodman and Gilman's, "The Pharmacological Basis of Therapeutics", 8th ed., McGraw-Hill, Inc. (1990), p. 518). The antitussive activity of dextromethorphan has led to its use in a variety of over-the-counter orally administered therapeutic compositions (tablets, syrups) for the relief of cold, influenza and/or cough conditions.

Many, if not most, of these therapeutics also contain a nonopioid analgesic such as an NSAID.

U.S. Patent No. 4,446,140 describes a method of treating mouth pain, i.e., pain or discomfort associated with the oral cavity, the teeth, gums and other mucosal surfaces of the lips, tongue and mouth resulting from such causes as toothache, denture irritations, canker sores, irritation related to inflamed gums, orthodontic tooth manipulation and appliances, oral surgery, etc., by administration of dextromethorphan alone or together with a conventional analgesic such as acetaminophen, indomethacin, ibuprofen or naproxen or a conventional anesthetic such as benzocaine or butacaine.

U.S. Patent No. 5,321,012 discloses that administration of a nontoxic NMDA receptor antagonist such as dextrorphan or dextromethorphan prior to, with or following administration of an opioid analgesic such as morphine, codeine, and the like, inhibits the development of addiction to and/or dependence on the analgesic.

European Patent Application 0 081 823 describes a method of temporarily reducing pain and discomfort associated with dysmenorrhea by administration of dextromethorphan alone or in combination with one or more additional drugs, e.g., an analgesic such as acetaminophen, indomethacin, ibuprofen or naproxen.

SUMMARY OF THE INVENTION

It has now been found that the analgesic effectiveness of known combination drugs containing at least one analgesic component can be significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate receptor antagonist thereto. In accordance with this invention, a

pain-alleviating drug composition is provided which comprises:

- 5 a) a pharmacologically effective amount of a first component which is a first analgesic selected from the group consisting of opioid analgesic and nonopioid analgesic;
- 10 b) a pharmacologically effective amount of a second component which is selected from the group consisting of sedative, skeletal muscle relaxant and, where the first analgesic is of the opioid type, a second analgesic of the nonopioid type; and,
- c) an analgesia-enhancing amount of a third component which is a nontoxic N-methyl-D-aspartate receptor antagonist.

15 The foregoing pain-alleviating drug composition is useful for treating a variety of chronic pain and acute pain states, e.g., arthritic pain, lumbosacral pain, musculoskeletal pain, post-operative pain and headache. When, in accordance with the method of the invention, e.g.,
20 a surgical procedure, the drug composition herein is administered to a mammal that is either experiencing pain, e.g., of the aforementioned kind, or is about to be subjected to a pain-causing event, e.g., a surgical procedure, the resulting level of pain relief is
25 significantly enhanced relative to that obtained with the same drug composition but one lacking the nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist component. This ability of the NMDA receptor antagonist component to enhance the efficacy of the analgesic component(s) of the drug
30 composition permits either a reduction in the amount of analgesic(s) in a dosage unit without a reduction in the level of pain relief or an increase in the level of pain relief without an increase in the amount of analgesic(s) in a dosage unit. Either capability offers essentially the
35 same advantage, i.e., less analgesic is required for

effective pain management. Given the adverse effects of the opioid and nonopioid analgesics noted above, such advantage is of considerable benefit to those requiring pain relief, particularly in relatively long term (e.g., 1-4 weeks) or
5 chronic pain situations.

The expression "analgesia-enhancing" refers to any significant improvement in analgesic effectiveness of an analgesic or combination of analgesics expressed in terms of the level of analgesia and/or its duration.

10 The expression "N-methyl-D-aspartate receptor" shall be understood to include all of the binding site subcategories associated with the NMDA receptor, e.g., the glycine-binding site, the phenylcyclidine (PCP)-binding site, etc., as well as the NMDA channel. Thus, the
15 invention herein contemplates the use of nontoxic substances that block an NMDA receptor binding site, e.g., dextrorphan or dextromethorphan, or that block the NMDA channel, e.g., a substance that blocks the magnesium or calcium channel.

The term "nontoxic" as used herein shall be
20 understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA for
25 administration to humans. The term "nontoxic" is also used herein to distinguish the NMDA receptor antagonists, or blockers, that are useful in the practice of the present invention from NMDA receptor antagonists such as MK 801 (the compound 5-methyl-10,11-dihydro-SH-dibenze[a,d] cyclohepten-
30 5,10-imine), CPP (the compound 3-[2-carboxypiperazin-4-yl] propyl-1-phosphonic acid) and PCP (the compound 1-(1-phenylcyclohexyl)piperidine) whose toxicities effectively preclude their therapeutic use.

The term "pain-alleviating" shall be understood
35 herein to include the expressions "pain-suppressing" and

"pain-inhibiting" as the invention is applicable to the alleviation of existing pain as well as the suppression or inhibition of pain which would otherwise ensue from an imminent pain-causing event.

- 5 The expression "combination drug" shall be understood herein to include any drug composition containing at least two therapeutically active components of which at least one is an opioid or nonopioid analgesic drug.

10 BRIEF DESCRIPTION OF THE DRAWINGS

- In the accompanying drawings, Figs. 1 and 2 are graphical presentations of experimental data comparing the analgesic effectiveness of known combination drugs with the same drugs additionally containing dextromethorphan hydrobromide in accordance with the invention and with dextromethorphan hydrobromide administered by itself.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

- The first component of the drug composition of this invention is a first analgesic which can be of the opioid or nonopioid type. Useful opioid analgesics include morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmeferene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine and their pharmaceutically acceptable salts. Useful nonopioid analgesics include the coal-tar analgesics, in particular, acetaminophen, and nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, their mixtures and their pharmaceutically acceptable salts.

The second component of the drug composition of this invention can be a sedative (a term used herein to refer to drugs that include not only the sedatives or sedative-hypnotics as such but all other drugs having a
5 sedative action), a skeletal muscle relaxant, a second analgesic which is of the nonopioid type when the first analgesic is of the opioid type or combinations of any of the foregoing. The sedatives include the barbiturate sedatives such as amobarbital, aprobarbital, butabarbital,
10 butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal, thiopental and their pharmaceutically acceptable salts and the nonbarbiturate sedatives include benzodiazepines having a sedative action such as
15 chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam and their pharmaceutically acceptable salts, H₁ antagonists having a sedative action such as diphenhydramine, pyrilamine, promethazine, chlorpheniramine, chlorcyclizine and their
20 pharmaceutically acceptable salts, neuroleptics such as droperidol and miscellaneous sedatives such as glutethimide, meprobamate, methaqualone, dichloralphenazone and their pharmaceutically acceptable salts. Skeletal muscle relaxants include baclofen, carisoprodol, chlorzoxazone,
25 cyclobenzaprine, methocarbamol, orphenadrine and their pharmaceutically acceptable salts.

The third component of the drug composition of this invention is a nontoxic NMDA receptor antagonist. Among the nontoxic substances that block the NMDA receptor
30 and as such are useful for enhancing the analgesic activity of the combination therapeutic in accordance with this invention are dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), their mixtures and their
35 pharmaceutically acceptable salts. Other useful nontoxic

substances that block the NMDA receptor include ketamine, memantine, pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid. Of the NMDA receptor antagonists, dextromethorphan is preferred for use herein due to its high degree of proven safety and its ready availability (as the hydrobromide salt). While dextrorphan and its pharmaceutically acceptable salts will also provide excellent results, it is not known to be in commercial manufacture at this time.

The amounts of first and second component present in a unit dose of the drug composition of this invention can be the same as those employed in comparable dosage forms of known combination drugs such as those previously mentioned. The amount of third component, i.e., the nontoxic NMDA receptor antagonist, will be at least that which is required to significantly enhance the analgesic effectiveness of the analgesic(s) present in the dose. Suitable amounts of NMDA receptor antagonist for a given composition and dosage form can be readily determined employing routine procedures. In general, amounts of NMDA receptor antagonist that will significantly enhance the analgesic effectiveness of the therapeutic composition herein can vary from about 10 to about 100, and preferably from about 15 to about 60, mg per unit dose.

All modes of administrations are contemplated for the drug composition of this invention, e.g., administration can be orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection. The drug composition will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, the composition can be formulated as a liquid, powder, elixir, injectable solution or suspension, etc. Formulations for oral use can be provided as tablets, caplets or hard capsules wherein the pharmacologically

active ingredients are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are mixed with an oleaginous medium, e.g., liquid paraffin or
5 olive oil.

Aqueous suspensions can include pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate,
10 polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with
15 long chain aliphatic alcohols, e.g, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monooleate or condensation products of ethylene oxide with partial esters derived from fatty
20 acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, e.g., ethyl-or-n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose,
25 saccharin or sodium or calcium cyclamate.

In addition to the components already cited, the drug composition herein can contain one or more other pharmacologically active components, e.g., caffeine (a stimulant), chlorpheniramine maleate (an antihistamine),
30 phenylephrine hydrochloride and phenylpropanolamine hydrochloride (decongestants) and isometheptene mucate (a sympathomimetic).

EXAMPLES 1-26

The following unit dosage forms are illustrative
of the pain-alleviating therapeutic composition of this
invention:

	<u>Example</u>	<u>Dosage Form</u>	<u>First Component (mg)</u>	<u>Second Component (mg)</u>	<u>Third Component (mg)</u>	<u>Additional Active Component(s) (mg)</u>
10	1	tablet	codeine phosphate (30)	acetaminophen (650)	dextromethorphan hydrobromide (30)	
15	2	tablet	hydrocodone bitartrate (5)	acetaminophen (500)	dextromethorphan hydrobromide (30)	
	3	tablet	codeine phosphate (30)	aspirin (325)	dextromethorphan hydrobromide (30)	
20	4	tablet	hydrocodone bitartrate (5)	acetaminophen (250)	dextromethorphan hydrobromide (30)	caffeine (30); chlorpheniramine maleate (2); phenylphrine hydrochloride (10)
25	5	tablet	hydrocodone bitartrate (5)	aspirin (500)	dextromethorphan hydrobromide (30)	
30	6	capsule	dihydrocodeine bitartrate (16)	acetaminophen (356)	dextromethorphan (30)	caffeine (30)
	7	tablet	dihydrocodeine bitartrate (16)	aspirin (356)	dextromethorphan hydrobromide (30)	caffeine (30)
35	8	syrup	codeine phosphate (10)	promethazine hydrochloride (6.25)	dextromethorphan hydrobromide (30)	
40	9	injectable	meperidine hydrochloride (25 per ml)	promethazine hydrochloride (25 per ml)	dextromethorphan hydrobromide (10 per ml)	
45	10	capsules	oxycodone hydrochloride (5)	acetaminophen (500)	dextromethorphan hydrobromide (30)	
50	11	tablet	oxycodone hydrochloride (4.5); oxycodone terephthalate (0.38)	aspirin (325)	dextromethorphan hydrobromide (30)	
55	12	caplet	pentazocine hydrochloride (12.5)	aspirin (325)	dextromethorphan hydrobromide (30)	
	13	tablet	pentazocine hydrochloride (12.5)	aspirin (325)	dextromethorphan hydrobromide (30)	
60	14	tablet	propoxyphene napsylate (100)	acetaminophen (650)	dextromethorphan hydrobromide (30)	

	<u>Example</u>	<u>Dosage Form</u>	<u>First Component (mg)</u>	<u>Second Component (mg)</u>	<u>Third Component (mg)</u>	<u>Additional Active Component(s) (mg)</u>
5	15	capsule	propoxyphene hydrochloride (65)	aspirin (389)	dextromethorphan hydrobromide (30)	caffeine (32)
10	16	caplet	acetaminophen (500)	diphenhydramine citrate (38)	dextromethorphan hydrobromide (30)	
15	17	tablet	acetaminophen (500)	diphenhydramine hydrochloride (25)	dextromethorphan hydrobromide (30)	
	18	capsule	acetaminophen (325)	dichloralphen-azone (100)	dextromethorphan hydrobromide (30)	isomet heptene mucate (65)
20	19	tablet	aspirin (650)	butalbital (50)	dextromethorphan hydrobromide (30)	
	20	tablet	acetaminophen (325)	butalbital (50)	dextromethorphan hydrobromide (30)	caffeine (40)
25	21	capsule	aspirin (325)	butalbital (50)	dextromethorphan hydrobromide (30)	caffeine (40)
30	23	tablet	aspirin (325)	methocarbamol (400)	dextromethorphan hydrobromide (30)	
	24	tablet	aspirin (325)	carisprodol (200)	dextromethorphan hydrobromide (30)	
35	25	tablet	codeine phosphate (16)	aspirin (325); carisprodol (200)	dextromethorphan hydrobromide (30)	
40	26	injectable	fentanyl citrate (50 µg (as base) per ml)	droperidol (2.5 per ml)	dextromethorphan hydrobromide (15 per ml)	

In each of these unit doses, the NMDA receptor antagonist dextromethorphan hydrobromide significantly enhances the analgesic activity of the analgesic component(s).

EXAMPLE 27

This example demonstrates the enhanced analgesic effects resulting from the addition of dextromethorphan hydrobromide (DEX) to a drug combination of known type, specifically, one containing as active ingredients codeine hydrochloride (COD) and acetaminophen (APAP).

Each test dosage was administered intra-gastrically to one of four groups (n=10) of test animals, adult male Sprague-Dawley rats each weighing from 350-400g. The analgesia produced by each drug was measured by the tail-flick test of Trujillo et al., Science, 251:85-87 (1991). Tail-flick latencies were tested at one and one half hours after oral administration on Day 1, Day 3, Day 5 and Day 8. Differences in post-administration tail-flick latencies across groups on a given test day were examined using a one-way analysis of variance (ANOVA) followed by post-hoc Waller-Duncan k-ratio t (WD) tests.

One of the following four dosages was administered twice a day to one of the test groups (all dosage amounts in mg/kg body weight): COD(30)+APAP(300), COD(30)+APAP(300)+DEX(50), DEX(50) and saline (control). The observed tail-flick latencies provided a measurement of the analgesic effect for each dosage over the eight day test period. As shown in Fig. 1 and as expected, the DEX(50) and saline (control) dosages were essentially ineffectual as analgesics. The COD(30)+APAP(300) dosage provided an initial response of moderate analgesia but declined significantly thereafter to the point that on Day 8, the dosage provided little effective analgesia. However, in the case of the COD(30)+APAP(300)+DEX(50) dosage, initial analgesic response was significantly higher than that of the COD(30)+APAP(300) dosage and while falling off, continued to provide a significant level of pain relief through Day 8.

EXAMPLE 28

Employing test procedures similar to those described in Example 27, this example shows the enhanced analgesic effects resulting from the addition of DEX to another drug combination of known type, this one containing
5 oxycodone (OXY) and APAP as its active ingredients.

One of the following two dosages was administered twice a day to one of two groups (n=10) of Sprague-Dawley rats: OXY(9)+APAP(585) and OXY(9)+APAP(585)+
10 DEX(50). As shown in Fig. 2, the OXY(9)+APAP(585) dosage provided an initial level of moderate pain relief and a slight increase therein over the next two days. From Day 3 on, analgesic effectiveness declined sharply and at Day 8, was negligible. In sharp contrast to this dose-response
15 profile, the OXY(9)+APAP(585)+DEX(50) dosage provided a similar level of initial analgesia but one which increased sharply through Day 3, remained at a high level through Day 5 and though declining thereafter, continued to provide a significant level of pain relief at Day 8.

20

WHAT IS CLAIMED IS:

1. A drug composition comprising:
 - a) a pharmacologically effective amount of a first component which is a first analgesic selected from the group consisting of opioid analgesic and nonopioid analgesic;
 - b) a pharmacologically effective amount of a second component which is selected from the group consisting of sedative, skeletal muscle relaxant and, where the first analgesic is of the opioid type, a second analgesic of the nonopioid type; and,
 - c) an analgesia-enhancing amount of a third component which is a nontoxic N-methyl-D-aspartate receptor antagonist.
2. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic and second component (b) is a nonopioid analgesic.
3. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic and second component (b) is a nonopioid analgesic selected from the group consisting of coal tar analgesic and nonsteroidal antiinflammatory drug.
4. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic and second component (b) is a sedative selected from the group consisting of barbiturate sedative and nonbarbiturate sedative.
5. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic selected from the group consisting of coal tar analgesic and nonsteroidal antiinflammatory drug and second component (b) is a sedative selected from the group consisting of barbiturate sedative and nonbarbiturate sedative.
6. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic and second component (b) is a skeletal muscle relaxant.

7. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic selected from the group consisting of coal tar analgesic and nonsteroidal antiinflammatory drug and second component (b) is a skeletal muscle relaxant.

8. The drug composition of Claim 1 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

9. The drug composition of Claim 2 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

10. The drug composition of Claim 3 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

11. The drug composition of Claim 4 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

12. The drug composition of Claim 5 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

13. The drug composition of Claim 6 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

14. The drug composition of Claim 7 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

15. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic selected from the group consisting of morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmeferene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine, their mixtures and their pharmaceutically acceptable salts, second component (b) is a nonopioid analgesic selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, their mixtures and their pharmaceutically acceptable salts and third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

16. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic selected from the group consisting of codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, propoxyphene, pentazocine, their mixtures and their pharmaceutically acceptable salts, second component (b) is a nonopioid analgesic selected from the group consisting of acetaminophen, aspirin, ibuprofen, their mixtures and their pharmaceutically acceptable salts and third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

17. The drug composition of Claim 5 wherein
second component (b) is a sedative selected from the group
consisting of butalbital, diphenhydramine,
dichloralphenazone, promethazine, droperidol, their mixtures
5 and their pharmaceutically acceptable salts and third
component (c) is selected from the group consisting of
dextrorphan, dextromethorphan, their mixtures and their
pharmaceutically acceptable salts.

18. The drug composition of Claim 7 wherein
10 second component (b) is a muscle relaxant selected from the
group consisting of methocarbamol, carisoprodol,
orphenadrine, chlorzoxazone, their mixtures and their
pharmaceutically acceptable salts and third component (c) is
selected from the group consisting of dextrorphan,
15 dextromethorphan, their mixtures and their pharmaceutically
acceptable salts.

19. A method for alleviating pain which comprises
administering to a mammal which is either experiencing pain
or is about to be subjected to a pain-causing event a pain-
20 alleviating amount of a drug composition comprising:

a) a pharmacologically effective amount of a
first component which is a first analgesic selected from the
group consisting of opioid analgesic and nonopioid
analgesic;

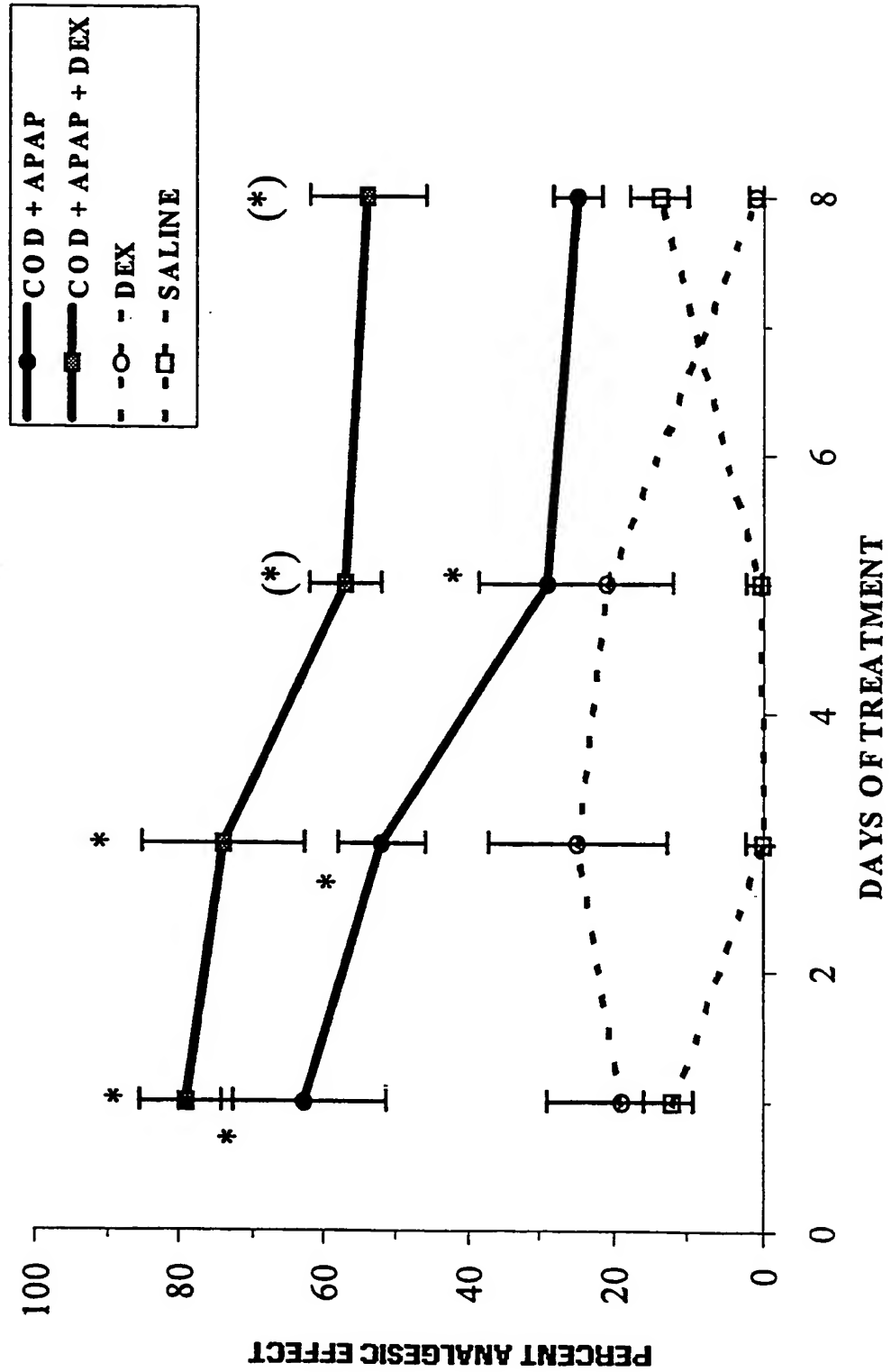
25 b) a pharmacologically effective amount of a
second component which is selected from the group consisting
of sedative, skeletal muscle relaxant and, where the first
analgesic is of the opioid type, a second analgesic of the
nonopioid type; and,

30 c) an analgesia-enhancing amount of a third
component which is a nontoxic N-methyl-D-aspartate receptor
antagonist.

20. The method of Claim 19 wherein the pain is
arthritic pain, lumbosacral pain, musculoskeletal pain,
35 post-operative pain or headache.

1 / 2

Figure 1.



2 / 2

Figure 2.

